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(54) Title: STENT WITH SUSTAINED DRUG DELIVERY

(57) Abstract

A mechanical support or stent containing pharmaceutical agents. The stent can be placed in the wall of a blood vessel where it releases pharmaceutical agents to prevent arterial thromboses, platelet aggregation and/or excessive endothelial cell proliferation at the placement site. The stent may also be placed in a blood vessel, bile duct, ureter, or fallopian tube or other duct or vessel, so that it delivers drugs to specific body sites or organs.

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DESCRIPTION

Stent With Sustained Drug Delivery

This invention relates generally to a mechanical support or stent containing pharmaceutical agents, and a method of using the same. More particularly, this invention relates to a stent containing pharmaceutical agents to be placed in a blood vessel where it preserves luminal dilation and releases agents that prevent arterial thrombosis, platelet aggregation, and/or excessive endothelial cell proliferation at the implant site; or to be placed in a blood vessel, bile duct, ureter, fallopian tube or other duct or vessel where it delivers pharmaceutical agents to specific body sites or organs.

Background

Despite steady progress in treatment and prevention, atherosclerotic cardiovascular disease remains the most common cause of death in industrialized countries. (AJR 150:1263-1269 (1988)). Although surgical methods of treating atherosclerosis, such as prosthetic replacement of the aorta and cardiac valves and coronary bypass surgery, have resulted in significant medical advancement, a need continues to exist for treatment with less expensive and less invasive techniques.

Percutaneous transluminal angioplasty (PTA), or balloon angioplasty, of peripheral and coronary arteries has proven to be a useful nonsurgical procedure for the treatment of localized occlusive arterial lesions due to atherosclerosis. (Merck Manual, 15th Ed., p. 559). The technique consists of inserting an uninflated balloon-tipped catheter into the affected artery. Dilation of the diseased segment of artery is accomplished by inflating the balloon which pushes the sclerotic lesion outward, thereby enlarging the arterial diameter. The balloon is then deflated and the catheter is withdrawn.

Following PTA, blood flow through the artery is typically significantly improved. Unfortunately, however, although more than 90% of dilations are initially successful, there is a high rate of early failure or later restenosis. About one-third of all patients treated with PTA return for a second or third procedure, thus reducing the long-term benefits of the procedure. (Eur. Heart J. 9:31-37 (1988)).

Some researchers have found most vessels that occluded after PTA revealed disrupted intima and a medial tear that extended to the internal elastic lamina, and that platelet deposition was extensive giving rise to early thrombosis. (Tex. Heart Inst. J. 15(1):12-16 (1988)). Longer balloon inflation times, high doses of calcium-channel blockers, steroids, and other drug regimens have been attempted, but so far have proved unsuccessful in combating this problem. (NEJM 316:701 (1987)).

To increase the long-term benefits of PTA, with the aim of preventing restenosis and sudden closure of diseased arteries after angioplasty, various intravascular prosthetic devices have been developed that can be placed across the freshly-dilated lesion.

Mechanical intraluminal stents have been suggested as an adjunct to PTA in the treatment of atherosclerosis. In 1969, Dotter et al., reported the first non-operative placement of coiled, stainless steel, wire stents in the arteries of dogs. (Invest. Radiol. 4:329-332 (1969). Fourteen years later, several reports on intravascular stents were published. (Radiology 147:261-263 (1983); Radiology 147:259-260 (1983); Radiology 152:659-663 (1984); Radiology 156:69-72 (1985); Radiology 156:73-77 (1985)). And recently Fischell et al. disclosed an invention for a coil spring intravascular stent. (U.S. Patent No. 4,768,507, issued September 6, 1988).

Intravascular stents function by opposing recoil of elastic vascular stenoses after angioplasty has failed.

They are also intended to provide a framework and support for arterial lesions that are likely to dissect after PTA. Although intravascular stents may be quite varied in design, they have been constructed of alloys of nickel and titanium (Id.), tempered stainless steel (Id.), plastic (Radiology 162:276-278 (1987)), or polyester (Tx. Heart Inst. J. 15:12 (1988)), and have three basic mechanisms of action: thermal memory, spring load, and plastic deformation. (AJR, 150:1263-1269 (1988)).

Stents have been used to maintain the patency of many other ducts or vessels as well. Stents placed in the ureter have been described for treatment of obstructions due to benign and malignant lesions. (J. of Urology 130:553-554 (1983)). As a method of nonoperative drainage in the case of obstructive jaundice, stents have been placed in the bile ducts for percutaneous drainage of the biliary system. (Gastrointest. Radiol. 10:394-396) (1985)).

Although most of the previously employed stents exhibited long-term patency of the vessel, failure commonly occurred when excessive endothelial cell growth caused significant narrowing of the lumen. (Radiology, 162:469-472 (1987)). In addition, thrombus formation in small diameter stents has been shown to reduce the lumen diameter and decrease blood flow. (Radiology 102:276-278 (1987)). A need exists therefore, for a stent that retains vessel patency as well as inhibits luminal narrowing.

To date, the placement of intravascular stents in humans has required extensive systemic anticoagulant treatment in an attempt to diminish thrombogenicity of the stents. Sigwart et al report the administration of oral anticoagulants (acenocoumarin) and antiplatelet drugs for at least three months following stent placement. (Eur. Heart J. 9:31-37 (1988)). As with many systemically administered anticoagulants, the chief complication is overdose and the resulting abnormal bleeding which

predisposes to massive hemorrhage if left unchecked. (Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., 1975). Because of this risk, improvements of stent technology are necessary.

Among the other complications encountered with the use of stents in humans were local spasms which occurred immediately after stent placement. To prevent these vasospasms, one researcher reports using nifedipine three times per day for three months. (Eur. Heart J., supra at 32.) Obviously avoidance of the systemic use of these antispasmotics would also be desirable.

Drug therapy now exists that can prolong useful life in persons diagnosed with cancer. Drug development for cancer began with the accidental identification of the antitumor activity of nitrogen mustard, and its success in the treatment of Hodgkin's disease and lymphocytic lymphomas. (Principles of Internal Medicine 9th Ed. p. 1601.) Since the 1950's when it was recognized that a standardized approach to the development of anticancer drugs was needed, many substances have been identified as having antitumor activity. Most of these drugs however, require systemic treatment which destroys cancer cells but also has adverse effects or toxicities on normal cells. A need continues for a method of drug delivery that would destroy cancer cells but not harm normal cells.

Additionally, the conventional methods of drug therapy, including tablets, capsules, slow-release formulations and injectables, all result in typical fluctuations of drug concentrations in the blood and body tissues. If the drug is in tablet or capsule form for example, it dissolves and releases the drug in high concentrations in the stomach; as the drug begins to be absorbed, its concentration in the body rapidly rises to a peak, followed by a decline related to its characteristic metabolism and elimination. With every dose of the drug, concentrations may alternately reach levels that produce adverse side effects and then decline

to values significantly less than therapeutic. As a result, in order to be effective, potent agents destined to treat specific organs must travel through the blood stream in much larger concentrations than those required at the target tissue. (Med. Res. Rev., 1(4):373-386 (1981)). A need exists therefore, for new types of drug delivery methods, to assure an adequate therapeutic effect while reducing or eliminating side effects.

Summary Of The Invention

The present invention provides a stent with sustained drug release capabilities which is believed to avoid the cited disadvantages of the prior art structures and methods.

Thus it is the objective of the present invention to provide an intravascular stent that preserves vessel patency and inhibits luminal narrowing.

A second objective of the invention is to provide a stent that can be placed in a vessel or duct and deliver a pharmaceutical agent to a specific body site or organ, thereby minimizing the systemic effect of these agents and adverse or toxic effects on other cells.

Detailed Description Of The Invention

The mechanical support or stent of this invention may be formed from any of the materials employed in the prior art that are non-toxic to the blood and body tissue and otherwise biocompatable. The stent may be in the form of any structure that successfully preserves the luminal diameter of a vessel or duct, and may operate by any mechanism known in the art.

The pharmaceutical agents suitable to be employed in this invention are too numerous to list. The agents may be anticoagulants, antiplatelet substances, antispasmodics or drugs that inhibit excessive endothelial cell growth, or they may be antimicrobial agents, hormones or anticancer drugs, or any combination of these agents, or

any others to accomplish any other localized purpose. The precise coating or impregnating of the stent with the pharmaceutical agent will vary depending on the form and material of the stent, and upon the pharmaceutical agent employed.

In use, the stent is placed into the vessel or duct so that it is in communication with the blood or other body fluid by means described in the art. A preferable means is the catheter insertion method as described by Fischell et al in U.S. Patent No. 4,768,507.

Thereafter, blood or other body fluids will come into contact with the stent which will release a sustained amount of the pharmaceutical agent at the placement site, and/or to specific tissues or organs.

In a preferred embodiment of the invention, an intravascular stent may contain heparin, aspirin, prostacyclin or an analog which when released by the stent, results in inhibition of thrombus formation or excessive endothelial cell growth.

In another embodiment, an intravascular stent may contain antitumor drugs, which, when released, result in antitumor activity.

By constructing a stent according to the above invention, several advantages may be realized. First, placement of the stent within a vessel will release anticoagulants, antiplatelet drugs or drugs that inhibit excessive endothelial cell growth at the placement site, thereby preserving the vessels patency and inhibiting luminal narrowing. Second, placement of a stent containing pharmaceutical agents, will deliver the agents to the placement site and/or to a specific body site or organ, thereby minimizing the systemic effect of these agents and adverse or toxic effects on other cells.

Other and further embodiments of the invention are readily apparent from the above description of the invention, and these embodiments are believed to be within the scope of the invention.

Claims:

1. A stent for placing in a vessel or duct which comprises:

a. a support means that preserves the luminal diameter of said vessel or duct; and

b. said means containing at least one pharmaceutical agent capable of sustained release from the stent.

2. A stent according to claim 1 wherein the vessel or duct is an artery, vein, bile duct, ureter, fallopian tube, or pancreatic duct.

3. A stent according to claim 1 wherein the support means is made of alloys of nickel and titanium, stainless steel, plastic or polyester.

4. A stent according to claim 1 wherein the support means functions to preserve the luminal diameter of a vessel by thermal memory, spring load or plastic deformation.

5. A stent according to claim 1 wherein the pharmaceutical agent is an anticoagulant, antiplatelet substance, antispasmotic, drug that inhibits excessive cell proliferation, antimicrobial agent, hormone, anti-tumor drug, calcium channel blocker or antiarhythmic drug.

6. A method for the sustained release of at least one pharmaceutical agent into a bodily fluid, which comprises:

a. placing a stent containing said pharmaceutical agent(s) into a vessel or duct;

b. said stent being in contact with the fluid in said vessel or duct; and

c. said stent thereby releasing said pharmaceutical agent(s) into said fluid.

7. A method according to claim 6 wherein the pharmaceutical agent is anticoagulant, antiplatelet substance, antispasmotic, drug that inhibits excessive cell proliferation, antimicrobial agent, hormone, antitumor drug, calcium channel blocker or antiarhythmic drug.

8. A method according to claim 6 wherein the bodily fluid is blood, urine or bile.

9. A method according to claim 6 wherein the stent is made of alloys of nickel and titanium, stainless steel, plastic or polyester.

10. A method according to claim 6 wherein the stent functions by thermal memory, spring load or plastic deformation.

11. A method acording to claim 6 wherein the vessel or duct is an artery, vein, bile duct, fallopian tube, or pancreatic duct.

12. A method according to claim 6 wherein the stent is placed into a vessel or duct by catheter insertion.

13. A method for treating atherosclerotic cardiovascular disease comprising:

a. placing a stent containing at least one pharmaceutical agent into a blood vessel;

b. said stent being in contact with the blood in said vessel; and

c. said stent thereby releasing said pharmaceutical agent(s) into said blood and to the placement site.

14. A method according to claim 13 wherein the stent is made of alloys of nickel and titanium, stainless steel, plastic or polyester.

15. A method according to claim 13 wherein the stent functions by thermal memory, spring load or plastic deformation.

16. A method according to claim 13 wherein the pharmaceutical agent is an anticoagulant, antiplatelet drug, antispasmotic, or drug that inhibits excessive endothelial cell proliferation.

17. A method according to claim 13 wherein the blood vessel is a peripheral or coronary artery.

18. A method according to claim 13 wherein the stent is placed into the blood vessel by catheter insertion.

19. A method for treating tumors comprising:

a. placing a stent containing a least one anti-tumor agent into a vessel or duct;

b. said stent being in contact with the fluid in the vessel or duct; and

c. said stent thereby releasing said antitumor agent(s) into said fluid and to said tumor.

20. A method according to claim 19 wherein the stent is made of alloys of nickel and titanium, stainless steel, plastic or polyester.

21. A method according to claim 19 wherein the stent functions by thermal memory, spring load or plastic deformation.

22. A method according to claim 19 wherein the vessel or duct is an artery, vein, bile duct, ureter, fallopian tube, or pancreatic duct.

23. A method according to claim 19 wherein the stent is placed into the vessel or duct by catheter insertion.

24. A method for treating a diseased organ or tissue comprising:

a. placing a stent containing at least one pharmaceutical agent into a vessel or duct;

b. said stent being in contact with the fluid in the vessel or duct; and

c. said stent thereby releasing said pharmaceutical agent(s) into said fluid and to said diseased organ or tissue.

25. A method according to claim 24 wherein the stent is made of alloys of nickel and titanium, stainless steel, plastic or polyester.

26. A method according to claim 24 wherein the stent functions by thermal memory, springload or plastic deformation.

27. A method according to claim 24 wherein the vessel or duct is an artery, vein, bile duct, ureter, fallopian tube, or pancreatic duct.

28. A method according to claim 24 wherein the pharmaceutical agent is an antimicrobial agent, or anti-tumor agent.

29. A method according to claim 24 wherein the stent is placed into the vessel by catheter insertion.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US90/02497

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61M 31/00
US 604/265, 606/191

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	606/191-200 604/890.1, 891.1, 892.1, 49.54,55,93,104,265,281,285 623/1.11,12,66

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X Y	PCT, B WO89/03232 (BUKH MEDITLC) 20 April 1989. See entire document.	1-16,18-29 17
X Y	US, A, 3,948,254 (ZAFFRONI) 06 April 1976. See entire document.	1-11,24-28 12-23,29
X Y	US,A, 3,279,996 (LONG, JR. ET AL.) 18 October 1966. See entire document.	1-11,13-17, 24-28 12,18,29
X Y	US, A, 4,321,711 (MANO) 30 March 1982. See entire document.	1-11,13-16, 24-28 17
X Y	US, A, 4,642,111 (SAKAMOTO ET AL.) 10 February 1987. See entire document.	19-22,24-28 23,29

* Special categories of cited documents: [15]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
26 JULY 1990	23 AUG 1990
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	ANTHONY M. GUTOWSKI

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